

The Tip of the Iceberg: A First Amendment Right To Promote Drugs Off- Label

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Scholars, advocates, and courts have begun to recognize a First Amendment right for the makers of drugs and medical devices to promote their products “off-label,” without proving safety and efficacy of new intended uses. Yet, so far, this debate has occurred in a vacuum of peculiar cases, where convoluted commercial speech doctrine underdetermines the outcome. Juxtaposing these cases against other routine prosecutions of those who peddle unapproved drugs reveals the common legal regime at issue. Review of the seven arguments deployed in the off-label domain finds that, if they were valid, they would undermine the FDA’s entire premarket approval regime. Even more, a companion paper shows that, if valid, this First Amendment logic would undermine a wide range of statutory regimes that have similar intent-based structures and that rely on speech as evidence of intent.

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I. INTRODUCTION

Unlike other regulatory systems, the Food, Drugs, and Cosmetics Act (FDCA) requires that *prior* to selling any drug or device intended to treat a disease, the seller must prove to the Food and Drug Administration (FDA) that it is in fact safe and effective.¹ If a company nonetheless sells such a drug or device without the FDA's approval and labeling, it commits a crime.²

By putting the burden of proof on drugmakers and device makers who can reap the profits from proven uses, this regulatory regime produces knowledge, which was not produced in the unregulated market that preceded it.³ With this science, physicians help patients make intelligent consumption decisions, and drug and device makers compete on proven quality rather than on hype. When this information is produced and released it creates a market whereby physicians, patients, and payors can evaluate whether a product is worth its price.

Some still debate whether this policy strikes the right balance to maximize aggregate social welfare.⁴ The cost of such a premarket approval regime is in the several years in which suffering and dying patients are generally unable to access drugs that *may or may not* someday be proven safe and effective.⁵ The

¹ 21 U.S.C. §§ 355(a)–(b)(1)(A), (d), 360e(c)(1); *see also* Christopher Robertson, Essay, *When Truth Cannot Be Presumed: The Regulation of Drug Promotion Under an Expanding First Amendment*, 94 B.U. L. REV. 545, 547–55 (2014) (reviewing this statutory regime).

² 21 U.S.C. § 331(a)–(d) (2012); *see also id.* § 333 (specifying felonies and misdemeanors); *id.* § 352 (defining “misbranding” and labeling requirements). Directions for use may be inadequate if “[s]tatements of all . . . uses for which such drug is intended” are omitted. 21 C.F.R. § 201.5(a)–(b) (2016); *see also id.* § 201.128 (referring to “the objective intent of the persons legally responsible for the labeling of drugs” and outlining the evidence that can show such intent).

³ *See* JOSEPH E. STIGLITZ, *ECONOMICS OF THE PUBLIC SECTOR* 79 (2d ed. 1988) (explaining that because information is a non-rivalrous and non-excludable public good, it can be expected to be insufficiently produced without regulatory intervention).

⁴ *See, e.g.,* Richard A. Epstein, *Against Permittis: Why Voluntary Organizations Should Regulate the Use of Cancer Drugs*, 94 MINN. L. REV. 1, 20 (2009).

⁵ Some patients may receive unapproved drugs through an “expanded access” program, through which the FDA quickly approves the vast majority of applications. Jonathan J. Darrow et al., *Practical, Legal, and Ethical Issues in Expanded Access to Investigational Drugs*, 372 NEW ENG. J. MED. 279, 279–80 (2015); *see also* 21 C.F.R.

benefit is a collective determination of *which* drugs really are safe and effective.⁶ The size of these costs and benefits is an empirical question, which must be compared against a counterfactual world in which patients would have broader access to drugs, but physicians and patients would have less information about their safety and efficacy.⁷

Legally, this regime focuses on the drugmaker and its intentions for its own product sold in interstate commerce. In contrast, federal law vests physicians and patients with broad discretion over the practice and consumption of medicine, understood historically as a primarily local behavior.⁸ In fact, physicians often prescribe drugs for “off-label” uses, beyond those approved by the FDA;⁹ in some clinical settings, virtually every prescription is written for an off-label use.¹⁰

Still, if a company intends to sell its product for these new uses too, the FDA requires that the company submit an application to change the label to reflect those intentions, supported by the same sorts of proof that the drug is in fact safe and effective for this new intended use.¹¹ Otherwise, the drug would be misbranded, failing to provide appropriate labeling for all intended uses.¹² This “intended uses” principle has reigned for decades.¹³ The FDA does not really

§ 312.300 (2016) (describing the limitations surrounding expanded access, aka “compassionate use”).

⁶ See generally Darrow et al., *supra* note 5, at 279–82 (describing the various actors involved in assessing the safety and efficacy of experimental drugs).

⁷ See David C. Radley et al., *Off-Label Prescribing Among Office-Based Physicians*, 166 ARCHIVES INTERNAL MED. 1021, 1021 (2006) (describing the dangers of off-label drug uses).

⁸ See 21 U.S.C. § 396 (2012) (“Nothing in this chapter shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship.”).

⁹ Radley et al. *supra* note 7, at 1021; Randall S. Stafford, Perspective, *Regulating Off-Label Drug Use—Rethinking the Role of the FDA*, 358 NEW ENG. J. MED. 1427, 1427 (2008).

¹⁰ See, e.g., Rebecca Dresser & Joel Frader, *Off-Label Prescribing: A Call for Heightened Professional and Government Oversight*, 37 J.L. MED. & ETHICS 476, 476 (2009) (“An off-label use may provide the best available intervention for a patient, as well as the standard of care for a particular health problem. In oncology, pediatrics, geriatrics, obstetrics, and other practice areas, patient care could not proceed without off-label prescribing.” (citations omitted)).

¹¹ 21 U.S.C. §§ 352, 355(a)–(b)(1)(A); see also 21 C.F.R. §§ 128, 201.5(a)–(b) (2016).

¹² Nathan Cortez, *The Statutory Case Against Off-Label Promotion*, 83 U. CHI. L. REV. ONLINE 124, 130–31 (2016); see also *supra* notes 1–2 and accompanying text.

¹³ See, e.g., *Alberty Food Prods. Co. v. United States*, 185 F.2d 321, 325–26 (9th Cir. 1950) (holding that a drug product was misbranded because its labeling failed to state the intended use of the drug as suggested by the company in newspaper advertisements).

approve drugs; it approves *uses* for drugs, one-by-one.¹⁴ In fact, roughly half of the applications submitted to the FDA are to seek approval for such new uses of old drugs, essentially bringing off-label uses on-label.¹⁵ In this way, the FDCA forces a drugmaker to internalize the cost of scientifically investigating the safety and efficacy of its own product insofar as the drugmaker intends to expropriate additional value from its product.

As the premarket approval policy is applied to new uses of approved drugs, the social welfare analysis is different, since patients can very easily access drugs “off-label,” even without FDA-approval. So, the welfare cost of the law is merely that physicians must rely on peer-reviewed articles and anecdotes from other physicians to learn about new uses, rather than on company promotional efforts. Physicians may adopt new uses more slowly than they otherwise would, but the effects are mixed since many of the new uses will turn out to be unhelpful or even deleterious on net. The welfare benefit of the policy is also attenuated in this domain, but the function remains the same as in the premarket approval process for new uses: the production of rigorous scientific knowledge about safety and efficacy, which helps physicians know *which* new uses to adopt.

The complicated welfare analysis is precisely the sort of policy question with which democratically-accountable legislatures and expert agencies must wrestle. Notably, Congress has already made the approval system more complex and flexible, with a range of statutory mechanisms that accelerate the availability of welfare-enhancing products to patients.¹⁶ And even prior to approval, the FDA has a fast and permissive mechanism, the expanded access exception, that allows patients to access promising drugs.¹⁷ There are various other tweaks that could be made to the policy that could advance or harm aggregate welfare. For example, one could raise or lower the level of evidence that the FDA requires to approve an indication, less often or more often allowing it to approve indications without randomized, controlled trials.¹⁸ Or, one could

¹⁴ See *Sigma-Tau Pharm., Inc. v. Schwetz*, 288 F.3d 141, 145 (4th Cir. 2002) (discussing the Orphan Drug Act amendments to the FDCA, explaining the words “for such disease or condition” suggests Congress intended to make section 360cc a “disease-specific, not drug-specific”); *Spectrum Pharm., Inc. v. Burwell*, 824 F.3d 1062, 1067 (D.C. Cir. 2016) (citing *Sigma-Tau Pharm.*, 288 F.3d at 145).

¹⁵ See Bo Wang & Aaron S. Kesselheim, *Characteristics of Efficacy Evidence Supporting Approval of Supplemental Indications for Prescription Drugs in United States, 2005–14: Systematic Review*, 351 BMJ 1–2 (2015), <http://www.bmj.com/content/bmj/351/bmj.h4679.full.pdf> [<https://perma.cc/ATQ5-BCJU>] (“In 2014 the FDA approved 40 new supplemental indications for already marketed drugs, compared with original approvals of 44 novel small molecule and biologic agents during the same period.”).

¹⁶ See, e.g., 21 U.S.C. § 356(a)–(c) (describing expedited approval for “breakthrough therapies” and “fast track drugs” to treat “serious or life-threatening diseases or conditions”); *id.* § 356-1 (describing “priority review” process for drugs expected to treat currently neglected or untreatable diseases).

¹⁷ 21 C.F.R. § 312.300 (2016); see also Darrow et al., *supra* note 5, at 279–80.

¹⁸ See e.g., Epstein, *supra* note 4, at 13 (questioning the value of clinical trials).

try to increase funding for the FDA to more quickly and/or more rigorously review applications submitted for new indications, building on the astounding progress already made in this regard.¹⁹

A few prominent scholars and advocates—and recently even some courts—have begun to recognize a First Amendment *right* for drugmakers to promote their products off-label, without proving safety and efficacy for the new use as the FDCA requires.²⁰ Constitutionalization of this question threatens to short-circuit the welfare debate. The Supreme Court has not yet resolved the question, but if it takes an off-label drug marketing case and embraces this same percolating First Amendment logic, it would allow a drugmaker to get FDA approval for any one use that it chose, but then promote the drug for every other use, even where safety and efficacy are unknown.²¹

The arc of constitutional history seems to be bending in this direction. There was a time when commercial speech, especially that proposing sale of a product, was not thought to receive First Amendment protection at all.²² In a landmark 1976 case, the Court found a right to advertise pharmaceutical drug prices.²³ In the 1980 *Central Hudson* case, the Court's doctrine solidified as it asked whether a commercial speech regulation “directly advances” a “substantial interest,” with means “not more extensive than necessary.”²⁴ In recent years, the

¹⁹ See Cassie Frank et al., *Era of Faster FDA Drug Approval Has also Seen Increased Black-Box Warnings and Market Withdrawals*, 33 HEALTH AFF. 1453, 1454, 1456 (2014) (documenting the false positives associated with faster review times resulting from prior legislation); John K. Jenkins, Director, FDA Office of New Drugs, Presentation at the FDA/CMS Summit: CDER New Drug Review: 2016 Update 20 (Dec. 14, 2016), <https://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm533192.pdf> [<https://perma.cc/HT33-MZMF>] (showing that median review times have been cut from over nineteen months to 7.8 months).

²⁰ See *infra* Part II for case examples and scholarly arguments limned in Part III *infra*.

²¹ See, e.g., Ed Silverman, *Two Former Device Maker Execs Go on Trial for Unauthorized Marketing*, STAT (June 6, 2016), <https://www.statnews.com/pharmalot/2016/06/06/device-fda-free-speech/> [<https://perma.cc/CW53-AP7E>] (expressing the prosecutors' theory that the company deceived the United States Food and Drug Administration by falsely claiming the intended use of a device to deliver saline when they actually intended it to deliver medicine). The executives were later convicted. Ed Silverman, *Former Execs at J&J Division Convicted of Illegally Distributing Devices*, STAT (July 20, 2016), <https://www.statnews.com/pharmalot/2016/07/20/medical-devices-fda-acclarent/> [<https://perma.cc/SE4H-YJS4>].

²² Sylvia A. Law, *Addiction, Autonomy, and Advertising*, 77 IOWA L. REV. 909, 927 (1992) (“Prior to 1976, . . . the prevailing constitutional doctrine . . . held that *all* product advertising ‘fall[s] outside the pale of First Amendment concern,’ or ‘at least [is] less rigorously protected than other forms of speech.’” (quoting *Banzhaf v. FCC*, 405 F.2d 1082, 1101 (D.C. Cir. 1968), *cert. denied*, 396 U.S. 842 (1969))).

²³ *Va. State Bd. of Pharmacy v. Va. Citizens Consumer Council, Inc.*, 425 U.S. 748, 770 (1976).

²⁴ *Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm’n*, 447 U.S. 557, 566 (1980); see also Aaron S. Kesselheim & Michelle M. Mello, *Prospects for Regulation of Off-Label*

Supreme Court has expanded the reach of the First Amendment in many domains—from video games²⁵ and animal-crush videos²⁶ to campaign finance²⁷ and military honors.²⁸ It has also eroded the line between “core” political speech that receives full First Amendment protection and commercial speech.²⁹ Scholars are now debating whether the First Amendment is, and should be, a generalized tool to promote an anti-regulatory agenda.³⁰

This Symposium Article systematically examines the First Amendment arguments for off-label promotion, and situates them in the larger scope of the FDCA premarket approval system. Part II juxtaposes recent challenges to the government’s authority to regulate drugs promoted for off-label uses against the government’s unobjectionable and little-noticed prosecutions of modern fraudsters, whose drugs have no FDA-approved indications at all. In both these off-label and no-label sorts of cases, the crime is the sale of a product with intent that it be used in ways not FDA approved. Yet, courts seem to be finding First Amendment rights in the off-label cases, but not in the no-label cases.

To test this disparity, Part III delves into the seven First Amendment arguments raised in the off-label domain to ask whether they apply equally to the no-label domain. In doing so, I flesh out the merits of each of these arguments, to test their applicability in these domains. For example, there is the threshold question of whether the FDA’s premarket approval system is

Drug Promotion in an Era of Expanding Commercial Speech Protection, 92 N.C. L. REV. 1539, 1589 (2014) (applying *Cent. Hudson Gas & Elec. Corp.*, 447 U.S. at 566).

²⁵ *Brown v. Entm’t Merchs. Ass’n*, 564 U.S. 786, 805 (2011).

²⁶ *United States v. Stevens*, 559 U.S. 460, 472 (2010).

²⁷ *Citizens United v. FEC*, 558 U.S. 310, 372 (2010).

²⁸ *United States v. Alvarez*, 132 S. Ct. 2537, 2551 (2012); see also Tim Wu, *The Right To Evade Regulation: How Corporations Hijacked the First Amendment*, NEW REPUBLIC 3, <https://newrepublic.com/article/113294/how-corporations-hijacked-first-amendment-evade-regulation> [<https://perma.cc/2T6Z-PHFL>] (describing this trend).

²⁹ Tamara R. Piety, “*A Necessary Cost of Freedom*”? *The Incoherence of Sorrell v. IMS*, 64 ALA. L. REV. 1, 4 (2012) (providing that the scrutiny of commercial speech regulations have “evolved into a strict scrutiny test in all but name”); see, e.g., *Sorrell v. IMS Health Inc.*, 564 U.S. 552, 579–80 (2011); see also Nathan Cortez, *Can Speech by FDA-Regulated Firms Ever Be Noncommercial?*, 37 AM. J.L. & MED. 388, 421 (2011) (exploring the core/commercial distinction in the pharmaceutical domain).

³⁰ E.g., RICHARD A. EPSTEIN, *THE CLASSICAL LIBERAL CONSTITUTION* 438 (2014) (arguing that economic regulations should receive heightened scrutiny as speech regulations appropriately do); MARTIN H. REDISH, *THE ADVERSARY FIRST AMENDMENT: FREE EXPRESSION AND THE FOUNDATIONS OF AMERICAN DEMOCRACY* 120–21 (2013) (“[O]pposition to commercial speech protection . . . all too often is [] a form of ideological hostility to the premises of capitalism and commercialism.”). See generally Jane R. Bambauer & Derek E. Bambauer, *Information Libertarianism*, 105 CAL. L. REV. 335 (2017) (reviewing the debate); Robert Post & Amanda Shanor, *Adam Smith’s First Amendment*, 128 HARV. L. REV. F. 165, 165–67 (2015) (discussing the use of Adam Smith’s economic theories as a rationale in the First Amendment case of *Edwards v. District of Columbia*, 755 F.3d 996 (D.C. Cir. 2014)).

regulating speech at all, or whether it is instead regulating the sale of a product in interstate commerce (a behavior), where the seller's speech is mere evidence of an illicit intent that the drug be used for an unapproved purpose.³¹ Since both no-label drugs and off-label drugs can otherwise be permissibly sold in interstate commerce, in both cases speech functions similarly to reveal a criminal intent, which transforms the behavior into something illicit. If it were problematic for the law to use speech as evidence of intent, it would seem to undermine the entire premarket approval regime. Similarly, for six other arguments asserted to support a First Amendment right to promote off-label, I show that if they were valid, they would also support a right to promote no-label.

A companion article examines laws in a wide range of other domains, from banking and bribery to guns and mining, which function similarly to the FDCA.³² In all these legal regimes, otherwise-legal behavior becomes criminal if done with an illicit intent, often proven by speech.³³ That survey suggests a broader difficulty for any reading of the First Amendment which creates a right to off-label promotion by denying the Government the power to use speech as evidence of intent.

II. RECENT CHALLENGES TO THE FDA'S PREMARKET APPROVAL SYSTEM

In a landmark 2012 decision, the United States Court of Appeals for the Second Circuit invoked the First Amendment to reverse a pharmaceutical sales representative's criminal conviction.³⁴ Although the jury found him guilty of conspiracy to sell a misbranded drug in interstate commerce, the defendant, Mr. Caronia, argued "that he was convicted for his speech—for promoting an FDA-approved drug for off-label use."³⁵ The Second Circuit agreed with that framing of the case, and said that it would "avoid constitutional difficulties by adopting

³¹ See *infra* Part III.A.

³² Christopher Robertson & Victor Laurion, *Tip of the Iceberg II: How the Intended-Uses Principle Produces Medical Knowledge and Protects Liberty*, 11 N.Y.U. J.L. & LIBERTY (forthcoming 2017) (manuscript at 20–26), <http://ssrn.com/abstract=2992668> [<https://perma.cc/EP86-W2VK>].

³³ See *id.*

³⁴ *United States v. Caronia*, 703 F.3d 149, 164–65 (2d Cir. 2012).

The Caronia case involved the powerful central nervous system depressant Xyrem (also known as the "date rape drug"), which had been approved for two specific indications based on randomized controlled trials that proved safety and efficacy in adults. Nonetheless, Mr. Caronia claimed that Xyrem was a "very safe drug," and recommended that physicians begin using Xyrem to treat a wide range of other diseases for both adults and children, including narcolepsy with cataplexy, excessive daytime and fragmented sleep, insomnia, fibromyalgia, periodic leg movement, restless leg, Parkinson's disease, muscular sclerosis, chronic fatigue, and chronic pain.

Robertson, *supra* note 1, at 553.

³⁵ *Caronia*, 703 F.3d at 152.

a limiting interpretation,”³⁶ which “construe[d] the misbranding provisions of the FDCA as not prohibiting and criminalizing the truthful off-label promotion of FDA-approved prescription drugs.”³⁷ Although the prosecution raised the argument that it was merely using the speech as evidence of an illegal intent, the *Caronia* court dismissed the point out of hand, suggesting that the prosecutors had referred to the speech too often to suppose that it was merely evidence of intent.³⁸ A powerful dissent challenged the majority’s reasoning as being myopic, without an understanding of the larger regulatory regime and First Amendment law.³⁹

Caronia upended decades of pharmaceutical law.⁴⁰ The FDA sought to minimize its impact by avoiding appeals and characterizing the case as limited to its facts, in which the prosecutors arguably failed to make clear that the salesman’s speech was merely being used as evidence of an illegal intent.⁴¹ Although the *Caronia* decision purported instead to rewrite the FDCA, many other off-label cases settled on terms that seemed to be favorable to the FDA even after *Caronia*.⁴²

In 2015, another drug maker, Amarin Pharma, invoked *Caronia* as precedent for a preliminary injunction against the FDA in the United States District Court for the Southern District of New York.⁴³ Amarin’s drug, Vascepa,

³⁶ *Id.* at 162 (quoting *Skilling v. United States*, 561 U.S. 358, 406 (2010)).

³⁷ *Id.* at 168.

³⁸ *Id.* at 160–61.

³⁹ *Id.* at 169–82 (Livingston, J., dissenting).

⁴⁰ *See, e.g.*, Whitaker v. Thompson, 353 F.3d 947, 953 (D.C. Cir. 2004) (“[T]he First Amendment allows ‘the evidentiary use of speech to establish the elements of a crime or to prove motive or intent.’ . . . Thus it is constitutionally permissible for the FDA to use speech, in the form of labeling, to infer intent for purposes of determining that [the plaintiff’s] proposed sale of saw palmetto extract would constitute the forbidden sale of an unapproved drug.” (quoting *Wisconsin v. Mitchell*, 508 U.S. 476, 489 (1993))).

⁴¹ *Caronia*, 703 F.3d at 161 (“The government never argued in summation or rebuttal that the promotion was evidence of intent.”).

⁴² *See, e.g.*, Press Release, U.S. Dep’t of Justice, Johnson & Johnson To Pay More than \$2.2 Billion To Resolve Criminal and Civil Investigations (Nov. 4, 2013), <https://www.justice.gov/opa/pr/johnson-johnson-pay-more-22-billion-resolve-criminal-and-civil-investigations> [<https://perma.cc/GB9X-Z96V>]; Press Release, U.S. Dep’t of Justice, Wyeth Pharmaceuticals Agrees To Pay \$490.9 Million for Marketing the Prescription Drug Rapamune for Unapproved Uses (July 30, 2013), <https://www.justice.gov/opa/pr/wyeth-pharmaceuticals-agrees-pay-4909-million-marketing-prescription-drug-rapamune-unapproved> [<https://perma.cc/G89N-NMXS>]. Still, the lower courts have begun to split on this question of whether off-label promotion is permitted, although most of that litigation does not squarely present the First Amendment issue. *See, e.g.*, *Jones v. Medtronic*, 89 F. Supp. 3d 1035, 1048 (D. Ariz. 2015) (agreeing with “the majority of courts in this Circuit . . . that the FDCA prohibits off-label promotion” but acknowledging a split among lower courts).

⁴³ *Amarin Pharma, Inc. v. U.S. FDA*, 119 F. Supp. 3d 196, 198 (S.D.N.Y. 2015).

had been approved by the FDA in July 2012 for use in treating adults with triglyceride levels above 500 mg/dL of blood, but Amarin sought to have the drug approved for use more broadly.⁴⁴ Notwithstanding some scientific support for such broader use, the FDA denied Amarin approval.⁴⁵ The FDA demanded evidence not only of a biological response to the drug, but a documented reduction in a health outcome, specifically cardiovascular risk.⁴⁶ In April 2015, the FDA issued a letter to Amarin notifying them that the company would need to provide such additional evidence before marketing the drug more broadly, and that Vascepa, “may be considered to be misbranded under the [FDCA] if it is marketed with this change before approval”⁴⁷

Invoking *Caronia*, Amarin challenged the FDA’s regulations, which prohibited them “from making completely truthful and non-misleading statements” about the product, as a violation of the First Amendment.⁴⁸ The FDA explained that its entire premarket approval system for drugs and devices, created by Congress in 1962, was at risk. The FDA sought to cabin *Caronia*, arguing that the case did not “preclude a misbranding action where the acts to promote off-label use consist solely of truthful and non-misleading speech, provided that the evidence also shows that the drug had been introduced into interstate commerce and that the FDA had not approved it as safe and effective for the off-label use.”⁴⁹ The court rejected the FDA’s arguments, explaining that the 1962 FDCA statute predates modern First Amendment case law, which protects truthful and non-misleading commercial speech.⁵⁰ The court again conceded that the government may use truthful speech as evidence of intent, but like the *Caronia* court, suggested that the prosecution was too focused on the speech itself to exploit that doctrine.⁵¹

In another case brought in the same district court, the FDA had sent Pacira Pharmaceuticals a letter reminding them that their drug, Exparel, was only approved for treating pain resulting from bunionectomies and hemorrhoidectomies and that the company should not promote the drug more

⁴⁴ *Id.* at 209 (“Amarin has sought approval to market Vascepa for patients with triglyceride levels between 200 and 499 mg/dL of blood and who are already on statin therapy”).

⁴⁵ *Id.*

⁴⁶ *Id.* at 211.

⁴⁷ *Id.* at 212. See generally Spencer Phillips Hey & Aaron S. Kesselheim, *An Uninformative Truth: The Logic of Amarin’s Off-Label Promotion*, PLOS MED. (2016), <http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1001978> [<https://perma.cc/SP3K-7QT3>] (arguing that even if truthful, the claims were uninformative and thus misleading).

⁴⁸ *Amarin*, 119 F. Supp. 3d at 212.

⁴⁹ *Id.* at 224.

⁵⁰ *Id.*

⁵¹ *Id.*

broadly.⁵² Pacira argued that the company had a First Amendment right to promote Exparel for unapproved and off-label uses.⁵³ The case quickly settled after the trial court decision in *Amarin*, with the FDA mooted much of the First Amendment concerns by agreeing to approve the drug for other post-surgical pain treatment as well.⁵⁴ After reaching the agreement, the FDA said that the revision in Exparel's labeling was based on previously submitted scientific evidence.⁵⁵

These off-label promotion cases should be viewed in the light of cases where there is no FDA-approved indication at all. Historically, these products were known as "snake oils" or "quackery," but as Daniel Carpenter explains, "[s]uch language might imply that the market for such medicines was a trifling sideshow to the emergence of medically prescribed pharmaceutical products in the economic history of the West. Nothing could be further from the truth."⁵⁶ Up until the time the FDCA was enacted, the market for "patent medicines" grew consistently from the colonial era to consume hundreds of millions of dollars in annual sales, based on widespread advertising in the leading periodicals of the time.⁵⁷

An example of such a product was "Hamlin's Wizard Oil," which consisted of turpentine and other proprietary ingredients, and was promoted to treat a wide range of ailments.⁵⁸ Decades later, another notable example was Amygdalin, a naturally-occurring substance used to treat cancer in Mexico and other parts of the world. The FDA has declined to approve a partially-synthesized version for use in the United States.⁵⁹ The compound, which contains cyanide, is thus a "no-label" product, even if it was recommended by some physicians.⁶⁰

The phenomenon continues, and continues to be prosecuted, today. For example, Conrad LeBeau was convicted in 2015 for introducing into interstate

⁵² *Pacira Pharm., Inc. v. U.S. FDA*, No. 15 Civ. 7055 (LAK), 2015 WL 9499516, at *5 (S.D.N.Y. Dec. 15, 2015) (stipulation and order of settlement).

⁵³ *Id.*

⁵⁴ *Id.* at *6; see also Brendan Pierson, *Pacira, FDA Reach Agreement on Pain Drug Marketing Restrictions*, YAHOO NEWS (Dec. 15, 2015), <http://news.yahoo.com/pacira-fda-reach-agreement-pain-drug-marketing-restrictions-050405009--finance.html> [<https://perma.cc/8XEP-VS8Y>].

⁵⁵ Pierson, *supra* note 54.

⁵⁶ DANIEL CARPENTER, REPUTATION AND POWER: ORGANIZATIONAL IMAGE AND PHARMACEUTICAL REGULATION AT THE FDA 77 (2010).

⁵⁷ *Id.*

⁵⁸ *United States v. Caronia*, 703 F.3d 149, 171 n.2 (2d Cir. 2012) (Livingston, J., dissenting).

⁵⁹ See *United States v. Rutherford*, 442 U.S. 544, 548 (1979); *Laetrile/Amygdalin (PDQ®)—Patient Version*, NAT'L CANCER INST., http://www.cancer.gov/about-cancer/treatment/cam/patient/laetrile-pdq/#link/_28 [<https://perma.cc/CML7-ULYC>].

⁶⁰ *Rutherford*, 442 U.S. at 556 (discussing the lower court's authorization of laetrile "under a doctor's supervision").

commerce a drug he called “Perfect Colon Formula #1,” which he claimed reduced food allergies, although it was not approved by the FDA.⁶¹ LeBeau invoked *Caronia* to argue that the FDCA unconstitutionally penalized him for speech about the use of a product, but the court rejected that theory, explaining that the statute prohibits the introduction of an unapproved drug into interstate commerce.⁶² LeBeau insisted that his claim that Perfect Colon Formula #1 “reduces food allergies” was neither misleading nor illegal.⁶³ The LeBeau court thought it important, however, that LeBeau’s drug had no approved uses at all, distinguishing that Mr. Caronia “was not prosecuted for distribution of an unapproved new drug. Instead, he had promoted an approved drug for off-label use.”⁶⁴ The trial court seemed to be invoking this as a per se distinction, without explicit reasoning.

In another case, Louis Daniel Smith was convicted in May 2015 for selling a product he called “Miracle Mineral Solution” (MMS) as a cure for cancer, AIDS, malaria, hepatitis, Lyme disease, asthma, and the common cold.⁶⁵ Some MMS promoters suggested it be swallowed orally or used as an enema to treat autism, as well.⁶⁶ In fact, MMS is a mixture of sodium chlorite,⁶⁷ an industrial chemical used as a pesticide and for hydraulic fracking.⁶⁸ Once consumers of MMS mixed the sodium chlorite with citric acid, as instructed, they had chlorine dioxide, an industrial-strength bleach.⁶⁹ At his trial, Smith argued that the First and Fourteenth Amendments protected his business model.⁷⁰ Although he did not specifically raise *Caronia* (perhaps because he was representing himself pro se), Smith contended that because the business had been conducted privately as

⁶¹ United States v. Lebeau, No. 10-CR-253, 2016 WL 447612, at *1 (E.D. Wis. Feb. 3, 2016).

⁶² *Id.* at *9.

⁶³ *Id.* at *8.

⁶⁴ *Id.* at *9.

⁶⁵ Press Release, Dep’t of Justice Office of Pub. Affairs, Seller of “Miracle Mineral Solution” Convicted for Marketing Toxic Chemical as a Miracle Cure (May 28, 2015), <http://www.justice.gov/opa/pr/seller-miracle-mineral-solution-convicted-marketing-toxic-chemical-miracle-cure> [<https://perma.cc/Z3MN-BP6A>].

⁶⁶ Guy Lynn & Ed Davey, ‘Miracle Autism Cure’ Seller Exposed by BBC Investigation, BBC NEWS (June 11, 2015), <http://www.bbc.com/news/uk-england-london-33079776> [<https://perma.cc/6L76-6NKE>]. The FDA referred to “miracle cures” in a consumer update warning of the rise in fraudulent treatments for autism, some of which carried dangerous health risks. *Autism: Beware of Potentially Dangerous Therapies and Products*, U.S. FDA (Apr. 25, 2014), <http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm394757.htm> [<https://perma.cc/NG8D-BRUZ>].

⁶⁷ *See id.*

⁶⁸ Dep’t of Justice Office of Pub. Affairs, *supra* note 65.

⁶⁹ *Id.*

⁷⁰ *See* Mark Freeman, ‘Miracle’ Providers Claim Constitutional Protection, MAIL TRIB. (Feb. 20, 2013), <http://www.mailtribune.com/article/20130220/NEWS/302200322> [<https://perma.cc/UWY5-G3K9>].

a “First Amendment Private Health Care Association,” the FDCA was not applicable.⁷¹ That argument failed.⁷²

These courts have blithely tolerated prosecutions of no-label drug dealers, even over First Amendment arguments. In many other cases, the defendant does not even raise the claim, or if raised, the claim does not appear in published opinions.⁷³ As Robert Post has written in other domains, “[i]t is not that regulation of this conduct is affirmatively permitted by the First Amendment; it is rather that courts do not even subject such regulation to First Amendment scrutiny.”⁷⁴

III. THE OFF-LABEL ARGUMENTS AND THEIR APPLICATION TO THE NO-LABEL DOMAIN

The review of recent cases suggests that it is infected by an untheorized incoherence. In the “off-label” cases, defendants successfully raise First Amendment arguments to avoid prison for promoting drugs for uses not approved by the FDA. In another set of “no-label” cases, defendants are being sent to prison for promoting drugs for uses not approved by the FDA. In both sets of cases, we have promotion for uses not approved by the FDA, but radically different outcomes.

Let us set up a running schema to illustrate the problem. Suppose there is a chemical compound, Offixa, which has been FDA approved to treat a condition, such as hair loss or macular degeneration. Suppose there is another chemical compound, Notixa, that has *not* been FDA approved for any purpose, but which is routinely sold in another domain, for example, as a cleaning product, nutritional supplement, or an industrial solvent. On the FDA’s view, if the makers of either Offixa or Notixa run ads saying, “my product cures cancer,” they express the intent that it be used as such, and commit a crime when they then sell their product.

How does the First Amendment apply in these two domains? Does it require that the FDA tolerate promotions for unapproved uses in one domain, but not the other? Consider each of the seven arguments asserted for a right to promote off-label.

⁷¹ *Id.*

⁷² See Dep’t of Justice Office of Pub. Affairs, *supra* note 65.

⁷³ See, e.g., *United States v. Scully*, 170 F. Supp. 3d 439, 454 (E.D.N.Y. 2016) (upholding a conviction for selling misbranded drugs in interstate commerce, relying partially on sales fliers, a form of speech).

⁷⁴ Robert Post, *Reconciling Theory and Doctrine in First Amendment Jurisprudence*, 88 CAL. L. REV. 2353, 2364 (2000).

A. *The Regulation of Speech*

The most fundamental argument advanced for a First Amendment right to promote drugs off-label is that such promotion is a form of speech.⁷⁵ This theory has some facial plausibility, since marketing efforts have for decades been well-understood to be a protected form of speech, and the Supreme Court has struck down speech regulations in the pharmaceutical sector in particular.⁷⁶ Some have argued that commercial speech should receive full First Amendment protection.⁷⁷ Alternatively, some argue that promotional speech is not purely commercial, but includes the exchange of information, often to learned intermediaries.⁷⁸ For present purposes, these points can be conceded; the question is merely whether the FDA is regulating speech at all in the off-label domain and in the no-label domain.

To the contrary, the FDCA arguably proscribes the *conduct* of selling a drug in interstate commerce with the intent for it to be used in ways that are not FDA approved and shown on the label with appropriate instructions for safe use.⁷⁹ On this view, prosecutions for violating this crime are not regulations of speech at all, since the speech is merely evidence of the drugmaker's intent to sell a product not proven safe and effective through the procedure Congress established. As I have explained elsewhere, the intent that a product be used to treat a disease is what makes it a drug, and that same predicate then creates the duty to prove its safety and efficacy.⁸⁰

This regime can be understood as a classic regulation of conduct (*actus reus*), with a *mens rea* (intent) element. As both the *Offixa* and *Notixa* examples show, the product may be sold in interstate commerce without this illicit intent (intending instead that it be used for an approved purpose or for some other

⁷⁵ See, e.g., *supra* notes 34–51 for a discussion of *Caronia* and *Amarin*.

⁷⁶ E.g., *Sorrell v. IMS Health Inc.*, 564 U.S. 552, 577–78 (2011) (“[T]he State may not seek to remove a popular but disfavored product from the marketplace by prohibiting truthful, nonmisleading advertisements”); *Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 374 (2002) (the Court has long “rejected the notion that the Government has an interest in preventing the dissemination of truthful commercial information in order to prevent members of the public from making bad decisions with the information”); *Va. State Bd. of Pharmacy v. Va. Citizens Consumer Council, Inc.*, 425 U.S. 748, 770 (1976) (providing that the state could not limit pharmacists’ advertising of drug prices).

⁷⁷ See, e.g., *REDISH*, *supra* note 30, at 121.

⁷⁸ See, e.g., Jennifer L. Herbst, *Off-Label “Promotion” May Not Be Merely Commercial Speech*, 88 TEMP. L. REV. 43, 83 (2015) (stating that the speech is a mixture of commercial and scientific speech); Joseph J. Leghorn et al., *The First Amendment and FDA Restrictions on Off-Label Uses: The Call for a New Approach*, 63 FOOD & DRUG L.J. 391, 397 (2008) (“[T]he underlying speech . . . is fully protected scientific speech.”).

⁷⁹ See *supra* notes 1, 2, 12 and accompanying text.

⁸⁰ See *Robertson*, *supra* note 1, at 547; see also 21 U.S.C. § 321(g)(1)(B)–(C) (2012) (incorporating the concept of intent in the definition of “drug”).

nondrug purpose altogether), and avoid criminal liability. In such cases, there is actus reus (sale) without illicit mens rea (intent for an unapproved use), and thus no crime. And likewise, those who speak, encouraging the use of a given drug for unapproved purposes, but do not sell it in interstate commerce, face no criminal liability. In such cases, there may be a mens rea but no actus reus, and thus no crime. The speech, on this theory, is not regulated whatsoever; the government regulates only acts with specific intent. The speech simply serves as evidence revealing a criminal intent, i.e., that a product be used for an unapproved purpose.

The Supreme Court has said that “[t]he First Amendment . . . does not prohibit the evidentiary use of speech to establish the elements of a crime or to prove motive or intent. Evidence of a defendant’s previous declarations or statements is commonly admitted in criminal trials subject to evidentiary rules dealing with relevancy, reliability, and the like.”⁸¹

After all, we have a specific rule of evidence allowing admission of statements of the defendant himself, even if it would be otherwise barred as hearsay.⁸² The Fifth Amendment also reflects this practice.⁸³ The Framers recognized that a defendant’s own speech could be used against him; they simply provided that such speech could not be compelled.⁸⁴ It is hard to imagine a stronger legal footing for the use of the defendant’s own speech against him.

As Richard Epstein has explained, “[t]he legal system could not operate if the external evidence of these mental states was systematically excluded from evidence, which of course it is not.”⁸⁵ Accordingly, the prosecution of a cocaine dealer based on a tapped phone call in which he proposes a sale does not implicate the First Amendment.⁸⁶ Even where there are expressive values at stake, such as when a person sends a letter to the government disclosing his criminal refusal to sign up for the military draft as required by law, a prosecution for the underlying crime does not violate the First Amendment.⁸⁷ Any impact on the First Amendment is “incidental,” and “[t]he First Amendment confers

⁸¹ *Wisconsin v. Mitchell*, 508 U.S. 476, 489 (1993). For an argument against this foundational rule, see Martin H. Redish & Michael J.T. Downey, *Criminal Conspiracy as Free Expression*, 76 ALB. L. REV. 697, 698–99 (2012/2013).

⁸² FED. R. EVID. 801(d)(2) (stating that “an opposing party’s statement” is excluded from hearsay and may be admissible).

⁸³ U.S. CONST. amend. V.

⁸⁴ See generally *Bram v. United States*, 168 U.S. 532, 542–43 (1897) (reviewing British and American history on the use of confessions); *Miranda v. Arizona*, 384 U.S. 436, 461–62, 467 (1966) (discussing *Bram*).

⁸⁵ EPSTEIN, *supra* note 30, at 438. See generally KENT GREENAWALT, *SPEECH, CRIME, AND THE USES OF LANGUAGE* 6–7 (1989) (reviewing many such crimes that involve language).

⁸⁶ See, e.g., *United States v. Carneiro*, 861 F.2d 1171, 1174 (9th Cir. 1988).

⁸⁷ See *Wayte v. United States*, 470 U.S. 598, 605, 611 (1985) (applying the *O’Brien* test for the “incidental” regulation of speech).

no . . . immunity from prosecution.”⁸⁸ The companion article documents innumerable other instances of speech being used as evidence of a criminal intent, making the FDCA’s regime quite routine.⁸⁹

In the off-label domain, challengers rejoin to the intent-conduct argument, saying that even when they do not promote off-label uses, drugmakers are often well *aware* of off-label uses of their product.⁹⁰ The challengers use this fact of company knowledge to show that the FDA turns a blind eye, and prosecutes only when the drugmakers *promote*. Thus, it is really a speech regulation after all.

To the contrary, the FDCA draws the line at *intent* for a new use, which is a distinct legal standard compared to knowledge or other potential mens rea elements Congress could have selected. This is not an uncommon move for legislators.⁹¹ In patent law, for example, “[m]ere knowledge of possible infringement by others does not amount to inducement; specific intent and action to induce infringement must be proven.”⁹² In the FDCA, Congress has a rational basis for choosing intent, since in the no-label context it allows use of chemicals for valuable nondrug purposes (for example, as industrial solvents or food additives), and in the off-label context allows physician discretion in the practice of medicine, which is outside the federal ambit. In both cases, the FDCA links the costs of scientific investigation to the manufacturer who intends to extract value from such medical uses.

Consider the alternative of using knowledge in the no-label context. In the recent case in which industrial bleach was being promoted by scam artists as a treatment for autism, discussed above,⁹³ the original chemical manufacturers may well have come to know that someone downstream was reselling their product for illicit purposes. Yet that knowledge alone is not tantamount to an

⁸⁸ *United States v. Fares*, 978 F.2d 52, 59 (2d Cir. 1992) (quoting *Wayte*, 470 U.S. at 614).

⁸⁹ See generally Robertson & Laurion, *supra* note 32.

⁹⁰ See, e.g., *United State v. Caronia*, 703 F.3d 149, 162 n.9 (2d Cir. 2012) (asking rhetorically if mere knowledge would impose liability); Coleen Klasmeier & Martin H. Redish, *Off-Label Prescription Advertising, the FDA and the First Amendment: A Study in the Values of Commercial Speech Protection*, 37 AM. J.L. & MED. 315, 343 (2011) (“The fact that a manufacturer fails to promote off-label use surely does not imply that it is *unaware* that its product will be used off-label; a drug manufacturer is not an idiot. Indeed, reimbursement for specified off-label uses of prescription drugs is well established.”) (emphasis added).

⁹¹ See, e.g., *Presbyterian Church of Sudan v. Talisman Energy, Inc.*, 582 F.3d 244, 259 (2d Cir. 2009) (“[T]he *mens rea* standard for aiding and abetting liability in [Alien Tort Statute] actions is purpose rather than knowledge alone.”).

⁹² *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1364 (Fed. Cir. 2003); see also *DSU Med. Corp. v. JMS Co.*, 471 F.3d 1293, 1306 (Fed. Cir. 2006) (en banc in relevant part) (providing that the inducement of infringement under Section 271(b) requires a “specific intent” to induce another to infringe).

⁹³ See Lynn & Davey, *supra* note 66.

intent that it be so used. There are innumerable other examples of products being diverted for illicit use—including pseudoephedrine being used to make methamphetamine⁹⁴ and glue being sniffed for a cheap high (aka “huffing”).⁹⁵ Prosecuting the chemical manufacturers—who know about but have done absolutely nothing to encourage these illicit uses—would be senseless. Moreover, if such a prosecution shut down the primary market to these products, it would deny access to all the other bona fide users of the chemical.

Similarly, in the off-label context, the makers of an approved cancer drug may well know that it will be used for other purposes, where it may even be the standard of care. But that mere knowledge has no causal effect on the world and does not implicate the drugmaker any more than it implicates strangers. In contrast, intent reflects the drugmaker’s attempt to expand sales into the new markets and then take responsibility for those marginal sales and profits. They are not mere windfalls, as they would be on a knowledge-based criterion. Accordingly, only when a manufacturer demonstrates that it *intends* to extract additional value by promoting their product for this new use, does Congress require that it make the investment to investigate scientifically whether it is safe and effective for that use.⁹⁶ The intentional claiming of those marginal sales brings with it the responsibility of proving their safety and efficacy.

Notably, even if the FDCA were rewritten to use knowledge as the predicate rather than intent, the exact same speech problem would arise, because it could be used as evidence of company knowledge. This argument is a complete red herring.

Accordingly, speech is simply one way that a manufacturer’s intent can be evinced.⁹⁷ A cocaine dealer’s intent to distribute can be shown by the amount he is carrying, his patterns of travel, and ultimately his act of making a delivery to a customer.⁹⁸ Similarly, a pharmaceutical drugmaker’s intent for their product to be prescribed for psychiatric disorders (regardless of whether it is so

⁹⁴ *Legal Requirements for the Sale and Purchase of Drug Products Containing Pseudoephedrine, Ephedrine, and Phenylpropanolamine*, U.S. FDA (Sept. 13, 2016), <https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm072423.htm> [<https://perma.cc/E88V-R9N4>].

⁹⁵ Nat’l Inst. on Drug Abuse, *Drug Facts: Inhalants*, DRUGABUSE.GOV, 1 (Feb. 2017), <https://www.drugabuse.gov/publications/drugfacts/inhalants> [<https://perma.cc/V6PP-JJD9>].

⁹⁶ *See, e.g.*, *United States ex rel. Duxbury v. Ortho Biotech Prods., L.P.*, 579 F.3d 13, 18, 32 (1st Cir. 2009); *United States ex rel. Bergman v. Abbot Labs.* 995 F. Supp. 2d 357, 361, 370 (E.D. Pa. 2014). *But see* *United States v. Caronia*, 703 F.3d 149, 152, 168 (2d Cir. 2012).

⁹⁷ *See* 21 C.F.R. § 201.128 (2016) (“[T]he objective intent of the persons legally responsible for the labeling of drugs” may be demonstrated by “oral or written statements by such persons or their representatives” and “the circumstances that the article is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised.”).

⁹⁸ *E.g.*, *United States v. Yearwood*, 518 F.3d 220, 226 (4th Cir. 2008).

approved) can be shown by the company hiring psychiatrists in key sales positions, by sending drug samples to psychiatrists, by subsidizing the psychiatry professional society, by paying kickbacks or other benefits to the psychiatrists who use the drug off-label, or by issuing coupons targeted to psychiatric patients in order to subsidize their consumption.⁹⁹ The drugmaker's speech is just one possible mechanism for showing the intended use; it is neither necessary nor always sufficient.¹⁰⁰

Still, this may all seem too formalist for the challengers—distinctions without differences.¹⁰¹ One must admit that speech plays a very prominent role in the typical misbranding prosecution. Accordingly, courts have summarily swept aside this theory.¹⁰² Some advocates have called it “disingenuous.”¹⁰³

Regardless of which side is correct on this point about whether the FDA is regulating speech or merely using it as evidence of intent, it should now be clear that the argument does *not* depend on whether the drug has been approved previously for a different use (as in off-label prosecutions) or not (as in no-label prosecutions). For Notixa, the exact same behavior of shipping in interstate commerce becomes criminal if the seller has and expresses an intent that it be used to treat an unapproved disease. Then it is a drug subject to FDA approval.¹⁰⁴ In this way, Notixa and Offixa rise and fall together. If either company claims that its product cures cancer, it will be liable for the crime of introducing a misbranded drug in interstate commerce. If neither company makes such a claim, then they are free to move their product in interstate commerce. There is no apparent theory of the First Amendment that would allow the FDA to regulate products using speech as evidence of intent in one category but not the other.

⁹⁹ See, e.g., *Duxbury*, 579 F.3d at 18 (rebate program as part of alleged scheme to encourage off-label use); *Bergman*, 995 F. Supp. 2d at 361 (kickbacks as part of an off-label marketing scheme).

¹⁰⁰ See *Amarin Pharma, Inc. v. U.S. FDA*, 119 F. Supp. 3d 196, 228 (S.D.N.Y. 2015) (“A manufacturer that engages in non-communicative activities to promote off-label use cannot use the First Amendment as a shield.”).

¹⁰¹ See, e.g., Rodney A. Smolla, *Off-Label Drug Advertising and the First Amendment*, 50 WAKE FOREST L. REV. 81, 111–12 (2015) (“The so-called ‘conduct’ being regulated is *expressive conduct*—conduct as protected by the First Amendment as moving one’s lips to talk.”).

¹⁰² See, e.g., *United States v. Caronia*, 703 F.3d 149, 161 (2d Cir. 2012) (rejecting the speech-as-evidence-of-intent doctrine because the prosecutors referred to the off-label promotion so often (“over forty times”)); *id.* at 159 (“Thus, the government’s theory of prosecution identified Caronia’s speech alone as the proscribed conduct.”).

¹⁰³ *Klasmeier & Redish*, *supra* note 90, at 342–43.

¹⁰⁴ See *supra* notes 1–15 and accompanying text.

B. Potential Truth of Efficacy

The Supreme Court has long said that commercial speech is unprotected if untrue.¹⁰⁵ In the off-label context, those who challenge the FDA emphasize that a company's claims about its product may in fact be true, and thus protected.¹⁰⁶ Maybe Offixa *does* cure cancer. But, maybe Notixa does too. The more important question is who should decide in either case?

I have elsewhere argued a point that should be obvious: we cannot simply assume (as courts and advocates have) that claims to off-label efficacy are true.¹⁰⁷ In fact, most off-label uses lack a strong scientific basis for inferring efficacy. In one recent study, the authors reviewed 17,847 off-label uses and found that 80.9% of the time, the uses "lacked strong scientific evidence."¹⁰⁸ This finding is similar to that of an often-cited 2006 national study by another team, finding that 73% of off-label uses had little or no scientific support.¹⁰⁹ Thus, quite often, off-label uses lack the scientific basis that the FDA requires

¹⁰⁵ See Gregory Conko, *Hidden Truth: The Perils and Protection of Off-Label Drug and Medical Device Promotion*, 21 HEALTH MATRIX 149, 151 (2011) (citing cases for the proposition that "the First Amendment does not protect false, fraudulent, or even unintentionally misleading speech"); see also Kesselheim & Mello, *supra* note 24, at 1577 (arguing that off-label promotion can be regulated where untrue). But see Constance E. Bagley et al., *Snake Oil Salesmen or Purveyors of Knowledge: Off-Label Promotions and the Commercial Speech Doctrine*, 23 CORNELL J.L. & PUB. POL'Y 337, 367 (2013) (it is difficult to discern whether commercial speech is truthful).

¹⁰⁶ See, e.g., Klasmeier & Redish, *supra* note 90, at 350 ("Government may not attempt to manipulate lawful citizen behavior by means of the selective suppression of truthful expression advocating lawful activity."); John E. Osborn, *Can I Tell You the Truth? A Comparative Perspective on Regulating Off-Label Scientific and Medical Information*, 10 YALE J. HEALTH POL'Y, L. & ETHICS 299, 307 (2010) ("[W]here the challenged off-label information is truthful, what is the public interest in forbidding it?"). See generally Stephanie M. Greene, Debate, *Off-Label Drug Promotion and the First Amendment: FDA Prohibitions on Off-Label Marketing Do Not Violate Drug Manufacturers' First Amendment Rights*, 162 U. PA. L. REV. ONLINE 239, 241–42 (2014) (introducing pharmaceutical manufacturers attempting to argue a First Amendment defense based on the fact that information provided by manufacturers is "truthful and not misleading"); Lars Noah, *Truth or Consequences?: Commercial Free Speech vs. Public Health Promotion (at the FDA)*, 21 HEALTH MATRIX 31, 37 (2011) ("[A]lthough the government may protect consumers from false or misleading information, it generally may not prohibit truthful and nondeceptive claims in pursuit of some other valuable ends."); Luke Dawson, Note, *A Spoonful of Free Speech Helps the Medicine Go Down: Off-Label Speech & the First Amendment*, 99 IOWA L. REV. 803, 814 (2014) (finding that speech "must concern lawful activity and not be misleading" (quoting *Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm'n*, 447 U.S. 557, 566 (1980))).

¹⁰⁷ See generally Robertson, *supra* note 1, at 558.

¹⁰⁸ Tewodros Eguale et al., *Association of Off-Label Drug Use and Adverse Drug Events in an Adult Population*, 176 JAMA INTERNAL MED. 55, 56–58 (2016).

¹⁰⁹ Radley et al., *supra* note 7, at 1021.

for new uses, on this score making them similar to new uses for unapproved drugs.

Of course, these same studies find that in a minority of cases, the off-label uses have a substantial scientific basis, perhaps even strong enough to support an inference that efficacy claims are truthful.¹¹⁰ This is just to say that the truth of efficacy claims about *that new indication* is supported by scientific investigation of *that indication*. Its truth has nothing to do with whether the drug is approved for some other indication. To be sure, the fact that Offixa was approved for hair loss does not make a claim that it cures bladder cancer any more or less true than the same claim that Notixa cures bladder cancer. In either case, if we are to infer truth of efficacy, someone would have to pay for an empirical investigation in front of a competent decision-maker and the burden of proof would be important, to weigh whatever evidence exists. In both the off-label and no-label cases, Congress has specified such a procedure and burden in the FDCA.¹¹¹ So, the epistemological argument—that maybe the efficacy claim is in fact true—threatens the entire premarket approval regime, if it threatens at all.

This division of epistemic labor is key. Congress has created an expert agency, with a specific process and standard for vetting the truth of claims about the safety and efficacy of drugs and devices.¹¹² In some cases, the agency has actually rejected a company's request for a new indication; in most other cases the company has declined to even ask, knowing that it cannot meet the agency's rigorous standards of proof. Does the First Amendment require that such truth claims be litigated in one branch of government versus another? Does it require a particular standard of proof? Arguably, no. As coequal branches, Congress and the FDA deserve the judiciary's deference for making factual determinations that would form the predicate for heightened constitutional scrutiny.¹¹³ Even more, for the task of determining the truth in this highly technical domain, the FDA has institutional advantages compared to the courts.¹¹⁴ These are heady doctrinal questions for the First Amendment, raising

¹¹⁰ Eguale et al., *supra* note 108, at 58 tbl. 1; Radley, *supra* note 7, at 1023.

¹¹¹ See 21 U.S.C. §§ 355(a)–(b)(1)(A), (d), 360e(c)(1).

¹¹² See generally Thomas W. Merrill, *Judicial Deference to Agency Action*, 9 ENGAGE 16, 17 (2008) (“[T]he courts will give very considerable deference to the fact findings of administrative agencies. . . . [T]here is no indication that the Court is posed to change the scope of review for questions of fact.”); Robertson, *supra* note 1, at 561 (developing an argument about this epistemic purpose of the FDA).

¹¹³ See *Holder v. Humanitarian Law Project*, 561 U.S. 1, 28, 34 (2010) (adopting strict scrutiny for First Amendment rights, but deferring to the government on empirical questions about threats posed by certain groups because of weighty national security interests involved and the Court's relative incapacity to make technical determinations).

¹¹⁴ See *Gonzales v. Carhart*, 550 U.S. 124, 163 (2007) (“The Court has given state and federal legislatures wide discretion to pass legislation in areas where there is medical and scientific uncertainty.” (citing *Marshall v. United States*, 414 U.S. 417, 427 (1974) (“When

questions not just about its scope but also about the role of the three branches to interpret and enforce its provisions.¹¹⁵ Whatever the answers may be to these big questions, they would not seem to differentiate between Offixa and Notixa.

To be sure, in the off-label context, there may be plausible biology stories about why a drug for one indication may work well for another. Yet, the same may be true for Notixa's cancer claim. It may have a plausible biological mechanism, may have a similar chemical structure to an approved drug, or may be approved in some other country. Both Offixa and Notixa may well be plausible candidates for a bladder cancer treatment. But plausibility is different than proof through established channels.

Here again, this logic does not supplant the FDA approval procedure, which can and does review data when determining the truth of efficacy claims, for the first indication or a subsequent one. The regulation of Offixas and Notixas rise and fall together.

C. *Proven Safety*

A third argument for the right to promote off-label asserts that the product has already been proven safe by the FDA's approval of the first labelled indication, so the FDA has no real interest in regulating further promotion of the product.¹¹⁶ At worst, the product may be ineffective for new indications, but it will assuredly be harmless. Why not let companies promote it for new uses?

Congress undertakes to act in areas fraught with medical and scientific uncertainties, legislative options must be especially broad”)); Edward M. Basile & Melanie Gross, *The First Amendment and Federal Court Deference to the Food and Drug Administration: The Times They Are A-Changin’*, 59 FOOD & DRUG L.J. 31, 43 (2004) (discussing *Thompson v. Whitaker*, 248 F. Supp. 2d 1 (D.D.C. 2002), where “the court went beyond its typical judicial practice and conducted its own analysis of the scientific data, ultimately substituting its interpretation of the data for the agency’s”).

¹¹⁵ See generally DAVID L. FAIGMAN, CONSTITUTIONAL FICTIONS: A UNIFIED THEORY OF CONSTITUTIONAL FACTS 111, 113 (2008) (exploring the “question [that] naturally arises [of] whether the Supreme Court ever owes deference to the factual resolves of juries, judges, legislatures, or administrative agencies;” describing how in one case, “the parties alternately argued that the Court owed deference to the fact-finding of legislatures or trial courts, depending on which institution supported its side of the case;” and noting that in that case, “[n]either side supplied a coherent explanation for its self-interested empirical jurisprudence”).

¹¹⁶ See Patricia J. Zettler & Henry T. Greely, *The Strange Allure of State “Right-To-Try” Laws*, 174 JAMA INTERNAL MED. 1885, 1885 (2014) (discussing “right-to-try” legislation motivated by a similar insight). See generally Daniel B. Klein & Alexander Tabarok, *Do Off-Label Drug Practices Argue Against FDA Efficacy Requirements? A Critical Analysis of Physicians’ Argumentation for Initial Efficacy Requirements*, 67 AM. J. ECON. & SOC. 743, 745, 768 (2008) (arguing that FDA’s premarket approval requirement to prove efficacy is inconsistent with its tolerance of off-label prescribing, and that the former should be eliminated).

Arguably, this factor distinguishes off-label use from no-label use, where there may have been no evidence of safety.

Before getting to high theory, the FDA starts by simply challenging the premise that a drug's safety proven for one indication demonstrates safety overall.¹¹⁷ Safety is a relative term; the law demands proven safety *for the intended uses*.¹¹⁸ This relativity is because we have much greater tolerance for a risky treatment for a terminal disease such as cancer, than for an acne treatment. The original, approved label is based precisely on a weighing of the risks and benefits of the drug for a given indication, and that balance may be completely different when used off-label. Indeed, the typical chemotherapy drug is patently unsafe, with onerous side effects including fatigue, pain, diarrhea, nausea, blood disorders, and nervous system effects. Other drugs have “black box” warnings because they are known to cause death in some populations. These nasty drugs are approved as “safe” only because, when used as indicated on the label, they have offsetting, proven benefits in the treatment of a specific disease.

Moreover, the FDA-approved indication is for a specific dose and method of delivery,¹¹⁹ all of which may be different when taken off-label. As toxicologists have recognized for centuries, the difference between a drug and a poison is simply the dose.¹²⁰ A drug approved for 10 milligrams administered as a topical cream may be utterly unsafe at 1,000 milligrams administered intravenously. In one case where a company promoted Botox as an off-label treatment for juvenile cerebral palsy, for example, a court upheld a jury's punitive damages award, finding that:

[T]he jury could have . . . reasonably concluded that [the company's] conduct was outrageously reprehensible because [the company] promoted the use of doses that it knew were risky in order to increase profits. . . . A reasonable jury could have felt morally outraged by a corporation's desire to put its bottom line above children's health, safety, and even lives.¹²¹

To simply presume the safety of off-label uses belies the facts of real cases.

More systematically, off-label use has been associated with adverse events. For example, Dr. Tewodros Eguale and colleagues conducted a cohort study across 46,000 patients and found that patients were more likely to suffer adverse drug events when using products off-label, and the difference was particularly stark when the use lacked a strong scientific basis in the form of a randomized,

¹¹⁷ See *infra* notes 118–25 and accompanying text.

¹¹⁸ See *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 612–13 (1973).

¹¹⁹ 21 C.F.R. § 201.5(b), (f) (2016).

¹²⁰ Philippe Grandjean, *Paracelsus Revisited: The Dose Concept in a Complex World*,

119 BASIC & CLINICAL PHARMACOLOGY & TOXICOLOGY 126, 126 (2016).

¹²¹ *Drake v. Allergan, Inc.*, 111 F. Supp. 3d 562, 577 (D. Vt. 2015).

controlled trial.¹²² No-label drugs also typically lack randomized, controlled trials showing safety and efficacy, and off-label drugs can be similarly dangerous. Aaron Kesselheim and colleagues conclude that,

Off-label drug prescribing has led to poor efficacy or harm in many instances in recent years, such as the use of nesiritide (Natrecor) for stable congestive heart failure, paroxetine (Paxil) for depression in children, antipsychotic drugs in elderly patients with dementia, and anti-epileptic medications for certain mood disorders. In each of these cases, patients were harmed by unsafe or ineffective off-label prescription drug use, which led to litigation. Manufacturers' promotional practices were found to have encouraged these off-label uses.¹²³

Of course, certain off-label usages are *in fact* perfectly safe. The point here is simply that one cannot *generally* infer safety of a drug for an indication other than the one that the FDA reviewed and approved.¹²⁴ There may be high-quality scientific studies showing safety for a particular use, and that will be true regardless of whether some other use is already approved. Just as in proof of efficacy, we have a legal procedure for an expert agency to make those inferences about safety when appropriate.¹²⁵

Putting all this aside, assume there is a constitutional right for drug companies to promote off-label use, based on the principle that the FDA has reviewed and approved the product's safety. The principle would seem to apply to at least some Notixas as well. Analytically, it is true that before *any* drug receives FDA approval, it is an unapproved drug, which cannot be marketed.¹²⁶ Indeed, over the lifetime of the FDA, thousands of drugs have passed the Phase I clinical trial process, which determines a dosage of the chemical in humans,

¹²² Egualé et al., *supra* note 108, at 56–58; see also Chester B. Good & Walid F. Gellad, *Off-Label Drug Use and Adverse Events: Turning Up the Heat on Off-Label Prescribing*, 176 JAMA INTERNAL MED. 63, 63–64 (2016) (discussing reports of harm from unapproved uses of drugs).

¹²³ Aaron S. Kesselheim et al., *Mandatory Disclaimers on Dietary Supplements Do Not Reliably Communicate the Intended Issues*, 34 HEALTH AFF. 438, 438 (2015) (citations omitted).

¹²⁴ Still, the FDA often considers *data* testing a drug for one indication as useful in assessing its safety for another. See, e.g., Wang & Kesselheim, *supra* note 15, at 5 (describing supplemental approvals for new pediatric indications “based on extrapolation from adult studies alone”).

¹²⁵ See *supra* notes 112–15 for a discussion of judicial deference to agency factual determinations.

¹²⁶ See generally Emily C. Feinstein et al., *The Ethics of Off-Label Use of FDA-Approved Products*, in OFF-LABEL COMMUNICATIONS: A GUIDE TO SALES & MARKETING COMPLIANCE 49, 49–51 (Mark Carlisle Levy ed., 4th ed. 2014) (discussing the distinction between marketing off-label uses and actually using drugs off-label in the context of FDA regulations).

one that is at least safe enough for broader testing (even if substantial safety risks remain).¹²⁷ Patients often demand access to such unapproved drugs, still in the process of being tested.¹²⁸ If there is a constitutional right to promote whatever is “safe” then it would arguably extend to this class of Notixas. Yet, allowing promotion at Phase II would of course eviscerate the very purpose of Phase III, which requires two well-controlled studies showing both safety and efficacy. Instead, the FDCA includes a “compassionate use” exception, which allows the FDA to grant access to these investigational drugs to certain patients, who have no other treatment options.¹²⁹ The courts have held that, outside this system, there is no substantive due process right to access experimental drugs—essentially rejecting the right here asserted in the off-label context.¹³⁰

Beyond the drug domain, federal law requires that the FDA review color additives for safety before they can be added to food, drugs, or cosmetics.¹³¹ Thus, on the challenger’s principle, could D&C Red #21 be promoted as a cure for cancer, diabetes, or acne because the FDA has approved it as safe for coloring drugs and cosmetics? Depending on how this theory is articulated, it may also apply to a wide range of foods, vitamins, and nutritional supplements that the FDA tolerates as presumably safe, although they are not subject to a premarket approval process. Can all these be touted as cures for cancer or hair loss?

If the theory is that the federal government cannot reach promotions of products that are *in fact* safe (regardless of the FDA), then it would embrace even more Notixas, such as the rare mineral water promoted as a cure for colitis, or the Chinese herbal teas promoted as a cure for cancer.¹³²

¹²⁷ See Michael J. Waring et al., *An Analysis of the Attrition of Drug Candidates from Four Major Pharmaceutical Companies*, 14 NATURE REVIEWS 475, 477 (2015) (showing that over a period of several years, of 145 drugs in Phase II trials, only 54 progressed to Phase III); *id.* at 479 (showing that about 25% of failures at Phase II are for safety, a rate similar to failures at Phase I).

¹²⁸ Darrow et al., *supra* note 5, at 279.

¹²⁹ 21 C.F.R. §§ 312.200–.320 (2016).

¹³⁰ See *Abigail All. for Better Access to Developmental Drugs v. von Eschenbach*, 495 F.3d 695, 703–07 (D.C. Cir. 2007) (en banc), *cert. denied*, 552 U.S. 1159 (2008). *But see* Richard A. Epstein, *The Erosion of Individual Autonomy in Medical Decisionmaking: Of the FDA and IRBs*, 96 GEO. L.J. 559, 577 (2008) (“[A] good libertarian, like me, has no difficulty in sustaining the [substantive due process] constitutional challenge to the FDA’s authority [in *Abigail Alliance*].”).

¹³¹ 21 U.S.C. § 379e (2012); *see also id.* § 321(t) (defining color additives).

¹³² See Press Release, Fed. Trade Comm’n, *FTC Sweep Stops Peddlers of Bogus Cancer Cures* (Sept. 18, 2008), <https://www.ftc.gov/news-events/press-releases/2008/09/ftc-sweep-stops-peddlers-bogus-cancer-cures> [<https://perma.cc/8SHL-8XR3>] (discussing enforcement against a company peddling Chinese teas for cancer); Harriet Hall, *The Water Cure: Another Example of Self Deception and the “Lone Genius,”* SCIENCE-BASED MED. (Jan. 12, 2010), <https://www.sciencebasedmedicine.org/the-water-cure-another-example-of-self-deception-and-the-lone-genius/> [<https://perma.cc/KLJ4-4XNE>].

Many Notixas are likely harmless, even if they are ineffectual and cause consumers to waste billions of dollars. One such (heavily litigated) example is saw palmetto, an herbal remedy, which has not received FDA approval as a treatment for mild benign prostatic hyperplasia.¹³³

The bottom line: if purported safety creates a right to promote off-label, the same theory would seem to apply to promotions of drugs and other products that have no FDA-approved labeling, but happen to have some evidence of safety. If valid, this principle undermines the premarket approval regime.

D. *The Litigation Alternative*

A fourth argument to support a right to promote off-label is to suggest that we do not need FDA regulation of off-label promotion because we have *other* legal mechanisms to protect against unsafe and fraudulent medical claims.¹³⁴ In particular, the Federal Trade Commission can prosecute those who would make false or misleading claims.¹³⁵ And since the federal government is a primary payor for health care, when it is defrauded by makers of drugs and devices it can also use the False Claims Act with the benefit of *qui tam* whistleblowers.¹³⁶ Individual patients can pursue products liability, false advertising, and fraud claims against manufacturers.¹³⁷ Or, in theory, patients could even sue their doctors for negligently recommending such a product when doing so is outside the standard of care. In short, since we have all these forms of litigation that are utterly unproblematic for the First Amendment, we do not need this worrisome form of off-label regulation.

Indeed, all of these mechanisms existed before the FDA was created to regulate safety and efficacy of the drugs through a premarket approval system.¹³⁸ In 1937, a drug containing diethylene glycol killed 107 persons; the next year Congress enacted the FDCA, requiring that new drugs be proven *safe* before entering the market.¹³⁹ In 1962, Congress passed the Kefauver-Harris

¹³³ See *Whitaker v. Thompson*, 353 F.3d 947, 953 (D.C. Cir. 2004); see also Stephen Bent et al., *Saw Palmetto for Benign Prostatic Hyperplasia*, 354 NEW ENG. J. MED. 557, 557 (2006) (no better than placebo).

¹³⁴ See, e.g., Epstein, *supra* note 4, at 11 (arguing that fraud litigation is an alternative to direct regulation of products).

¹³⁵ See, e.g., Smolla, *supra* note 101, at 108 (arguing that prosecutions for false or misleading advertising are an alternative to misbranding prosecutions).

¹³⁶ See 31 U.S.C. §§ 3729(a)–3730(c) (2012).

¹³⁷ See, e.g., *Wyeth v. Levine*, 555 U.S. 555, 558–59 (2009); Kaspar J. Stoffelmayr, Comment, *Products Liability and “Off-Label” Uses of Prescription Drugs*, 63 U. CHI. L. REV. 275, 281 (1996).

¹³⁸ See W. B. Rankin, *The Future Relationships of FDA and the Pharmaceutical Industry*, 20 FOOD DRUG COSM. L.J. 632, 632 (1965).

¹³⁹ See *Significant Dates in U.S. Food and Drug Law History*, U.S. FOOD & DRUG ADMIN. (Dec. 19, 2014), <http://www.fda.gov/AboutFDA/WhatWeDo/History/Milestones/>

amendments, which required advance proof of minimal *efficacy* as well.¹⁴⁰ These laws were passed on the theory that backwards-looking enforcement and litigation were insufficient.¹⁴¹ In particular, in terms of when, who, and where, the FDCA departs from these other mechanisms in three primary ways: (a) safety and efficacy must be proven before marketing, (b) the manufacturers have the burden of making that proof, and (c) the proof must be evaluated by an expert agency, the FDA.¹⁴² In these other forms of litigation, the quality of the drug would not necessarily be investigated until the litigation commenced, and the plaintiff or prosecutor would bear the burden of proving, to the nonspecialist judge or jury, the negative—that the product is dangerous, ineffective, or both.

One may debate whether each of these institutional features is optimally designed to promote innovation and protect the public health. We have already touched on the sensibility of putting the burden on the company that seeks to extract value from its own product (b) and why it is sensible to have an expert agency make that determination (c).¹⁴³ From the First Amendment perspective in particular, one could object that requiring proof in advance of marketing (a) functions as a “prior restraint,” one of the most worrisome forms of regulation, squelching ideas before they are even aired.¹⁴⁴ There is some debate about whether this doctrine is applicable in the commercial speech domain.¹⁴⁵ Indeed, in the pivotal *Central Hudson* case concerning the advertising of utility services, the Court actually recommended such a pre-approval approach, building on a

ucm128305.htm [https://perma.cc/82CD-YBN7].

¹⁴⁰ Jeremy A. Greene & Scott H. Podolsky, *Reform, Regulation, and Pharmaceuticals—The Kefauver-Harris Amendments at 50*, 367 NEW ENG. J. MED. 1481, 1481 (2012).

¹⁴¹ See *id.* at 1481–82.

¹⁴² See *id.*

¹⁴³ See *supra* Parts I–III.C.

¹⁴⁴ See, e.g., Krista Hessler Carver, *A Global View of the First Amendment Constraints on FDA*, 63 FOOD & DRUG L.J. 151, 179 (2008) (arguing that “[t]raditional First Amendment doctrine erects a ‘heavy presumption’ against the validity of a prior restraint on noncommercial speech”); Kristie LaSalle, Note, *A Prescription for Change: Citizens United’s Implications for Regulation of Off-Label Promotion of Prescription Pharmaceuticals*, 19 J.L. & POL’Y 867, 893 (2011) (arguing that under the Court’s holding in *Citizens United*, the FDA’s ambiguous regulatory scheme functions as a prior restraint); Kyle Thomson, *The Changing Landscape of the Commercial Speech Doctrine and FDA Advertising Regulation: Off-Label Marketing in the Wake of Sorrell v. IMS* 26 (May 31, 2012) (unpublished manuscript), <http://ssrn.com/abstract=2071226> [https://perma.cc/NTK4-JR3E] (noting that it could be argued that the “FDA’s current practice is ‘amorphous’ in the way the Court in *Citizens United* defines it, and, as such, acts as a prior restraint on any potential promotional speech by a drug manufacturer”).

¹⁴⁵ See Robert Post, *The Constitutional Status of Commercial Speech*, 48 UCLA L. REV. 1, 5 (2000) (arguing that “commercial speech doctrine does not prohibit . . . prior restraints”); *id.* at 32 (quoting Justice Blackmun in *Virginia State Board of Pharmacy* for the proposition).

precedent for prior review in the domain of obscenity law.¹⁴⁶ Compared to utility company advertising or obscenity, the stakes are extremely high in the medical drug and device domain—life and death for sick patients who are sometimes so desperately ill that they are particularly vulnerable to irresponsible marketing. So, maybe this is the rare domain where a prior restraint on speech can survive constitutional scrutiny (assuming that it is a regulation of speech at all).

Aside from the merits of this argument, all three of these elements (a, b, and c, enumerated above) apply equally in the domain of off-label and no-label prescribing. The same FDA review process and burden on the manufacturer applies to the first use of a drug and its tenth use. And we have the same regulatory alternatives—the Federal Trade Commission, a *qui tam* relator, or an injured patient can all go after no-label promoters or prescribers, just as they can off-label promoters and prescribers. If these avenues for litigation somehow undermined the FDA’s authority to regulate claims for Offixa, they would seem to do the same for Notixa.

E. Paternalism

A fifth argument asserted for the right to promote off-label says that the FDA is acting paternalistically, aiming to protect patients from making poor consumption decisions based on what they (or their physicians) hear in the promotions.¹⁴⁷ Depending on one’s political theory, paternalism may or may not be a permissible basis for regulation generally, but many find that paternalism is inappropriate as a basis for speech regulation in particular.¹⁴⁸ As David Strauss reads the doctrine, “the government may not justify a measure

¹⁴⁶ *Cent. Hudson Gas & Elec. Corp.*, 447 U.S. at 571 n.13 (“The Commission also might consider a system of previewing advertising campaigns to insure that they will not defeat conservation policy. It has instituted such a program for approving ‘informational’ advertising under the Policy Statement challenged in this case. We have observed that commercial speech is such a sturdy brand of expression that traditional prior restraint doctrine may not apply to it. And in other areas of speech regulation, such as obscenity, we have recognized that a prescreening arrangement can pass constitutional muster if it includes adequate procedural safeguards.” (citations omitted)).

¹⁴⁷ See, e.g., Noah, *supra* note 106, at 31–32 (stating the paternalism objection); Thea Cohen, Note, *The First Amendment and the Regulation of Pharmaceutical Marketing: Challenges to the Constitutionality of the FDA’s Interpretation of the Food, Drug, and Cosmetics Act*, 49 AM. CRIM. L. REV. 1945, 1966–67 (2012) (stating the paternalism objection).

¹⁴⁸ E.g., Elena Kagan, *Private Speech, Public Purpose: The Role of Governmental Motive in First Amendment Doctrine*, 63 U. CHI. L. REV. 413, 414 (1996) (“First Amendment law . . . has as its primary, though unstated, object the discovery of improper governmental motives. The doctrine comprises a series of tools to flush out illicit motives and to invalidate actions infected with them.”).

restricting speech by invoking harmful consequences that are caused by the persuasiveness of the speech.”¹⁴⁹

Of course, one need not concede that the FDA’s premarket approval system for intended uses of products is a speech regulation at all.¹⁵⁰ But, assuming that it is a speech regulation, the premarket approval system is not necessarily paternalistic. A paternalist would claim to know what behaviors will be good or bad for a consumer and use a regulation to shape her consumption accordingly, but the FDA does not know whether any given product will be safe and effective for a given use. That ignorance is actually the whole point of the regulatory regime; it exists to produce knowledge.¹⁵¹

The FDCA requires sellers of drugs to provide safety and efficacy evidence to support each intended use for the purpose of producing that knowledge for the consuming public.¹⁵² There is a large collective action problem; no individual patient or doctor would find it rational or feasible to do such scientific studies to determine safety and efficacy.¹⁵³ Yet talk is cheap. Without a well-powered controlled trial, like the ones required by Congress in the FDCA, it is impossible to reliably distinguish the drug’s effects from the natural course of the disease or sheer luck.¹⁵⁴ The FDCA solves the collective action problem and creates a functioning market for quality drugs by putting the burden of scientific research on the company who seeks to exploit the economic value of those intended uses.¹⁵⁵ It does so by prohibiting them from selling for intended uses that have not benefitted from such scientific investment.¹⁵⁶ On this view, the

¹⁴⁹ David A. Strauss, *Persuasion, Autonomy, and Freedom of Expression*, 91 COLUM. L. REV. 334, 334 (1991); see also Klasmeier & Redish, *supra* note 90, at 344 (“[S]uch paternalistic manipulation of consumer behavior is inconsistent with the very premises underlying democracy, let alone the constitutional guarantee of free expression, and no holding of the Court since at least the mid 1990s is inconsistent with this theory.”); Richard A. Samp, *Courts Are Arriving at a Consensus on Food and Drug Administration Speech Regulation*, 58 FOOD & DRUG L.J. 313, 324 (2003) (“The Supreme Court has never accepted the notion that truthful speech can be regulated in order to prevent harm where the sole embodiment of that harm is the speech itself.”).

¹⁵⁰ See *supra* Part III.A.

¹⁵¹ See Robertson, *supra* note 1, at 558–65 (discussing this epistemic and economic purpose for the FDA); Robertson & Laurion, *supra* note 32 (manuscript at 5–16) (developing the case study of Seroquel XR to show how the premarket approval system produces knowledge).

¹⁵² See Robertson, *supra* note 1, at 547.

¹⁵³ See generally STIGLITZ, *supra* note 3.

¹⁵⁴ 21 C.F.R. § 314.126 (2016).

¹⁵⁵ Cf., EPSTEIN, *supra* note 30, at 439 (noting resolution of a similar question where antitrust law sought to encourage competition “is wholly consistent with the First Amendment objective of pursuing competition in the marketplace of ideas”).

¹⁵⁶ See 21 U.S.C. §§ 355(a)–(b)(1), 360e(c)(1).

regime is not paternalism; it is value creation. In this way, it is not unlike the system of patent law, which also proscribes sale to encourage innovation.¹⁵⁷

Here again, we need not resolve whether the FDA's response to the paternalism argument is satisfactory. We need only observe that Offixa and Notixa rise together. The ban on no-label promotion (i.e., the entire premarket approval regime) is equally paternalistic—or not—as the ban on off-label promotion. In both cases, sellers are prohibited from marketing drugs that have not been proven safe and effective for their intended uses, and in both cases, patients also have physicians to protect their interests. Whether the FDCA's regime is characterized as paternalistic or as solving a collective action problem to produce knowledge, the characterization would apply to both cases.

F. *Discrimination*

A sixth argument for a right to promote off-label says that the FDA discriminates between the seller of the drug and others, such as physicians or layperson authors, who may speak emphatically in favor of the unapproved use.¹⁵⁸ In First Amendment doctrine, “viewpoint discrimination” is forbidden.¹⁵⁹ However, it is sometimes difficult to tell when the predicate applies to a particular regulation.¹⁶⁰ (Arguably, the rules on off-label promotion

¹⁵⁷ Patent law creates incentives for inventors to advance and disclose scientific knowledge by allowing only the inventor to reap the economic value of the product during the patent period. See Rebecca S. Eisenberg, *The Problem of New Uses*, 5 YALE J. HEALTH POL'Y L. & ETHICS 717, 720 (2005) (“Patent protection on drugs typically begins and ends too early to permit firms to capture the full value of subsequently developed information about drug effects. It therefore does a better job of motivating the initial R&D that is necessary to bring new products to market than it does of motivating the development of new information about old drugs.”).

¹⁵⁸ See Smolla, *supra* note 101, at 102 (similar); Ralph F. Hall & Elizabeth S. Sobotka, *Inconsistent Government Policies: Why FDA Off-Label Regulation Cannot Survive First Amendment Review Under Greater New Orleans*, 62 FOOD & DRUG L.J. 1, 28–29 (2007) (raising the discrimination problem); Lise T. Spacapan & Jill M. Hutchison, *Prosecutions of Pharmaceutical Companies for Off-Label Marketing: Fueled by Government's Desire To Modify Corporate Conduct or Pursuit of a Lucrative Revenue Stream?*, 22 ANNALS HEALTH L. 407, 420 (2013) (arrangement between manufacturers and physicians creates an asymmetric regulatory system); Jared Iraggi, Comment, *The Future of Off-Label Marketing Regulations in the Post-Sorrell Era*, 43 SETON HALL L. REV. 1137, 1157 (2013) (raising the discrimination problem).

¹⁵⁹ See Martin H. Redish, *Commercial Speech, First Amendment Intuitionism and the Twilight Zone of Viewpoint Discrimination*, 41 LOY. L.A. L. REV. 67, 69 (2007) (stating that viewpoint discrimination is “the most universally condemned threat to the foundations of free expression”).

¹⁶⁰ See Robert C. Post, *Viewpoint Discrimination and Commercial Speech*, 41 LOY. L.A. L. REV. 169, 169 (2007) (“[T]he concept of ‘viewpoint discrimination’ is . . . confused and uncertain,” and “there are good, non-viewpoint-based reasons for extending to commercial speech forms of protection that differ from those extended to political speech.”).

are more of a speaker-discrimination than a viewpoint-discrimination, but in this context the manufacturer is likely to have a particularly positive view about its product, making the points converge.)

Notably, the alleged discrimination created by the FDCA statute is not absolute. Companies may distribute reliable peer-reviewed publications about off-label uses and respond to questions from physicians without necessarily revealing an intent for the drug to be used off-label.¹⁶¹ These “safe harbors” for scientific communication about off-label uses arguably moot much of the concern that physician and patient are deprived of important information.¹⁶² But the safe harbors are narrow, and do not include puffery or emotive appeals that may be protected by the First Amendment.¹⁶³

Nonetheless, historically, the speech of drug manufacturers has been treated quite differently than the speech of doctors, patients, journalists, or academics. One could argue that the law properly disfavors the speech of the drug manufacturer, because it is likely biased towards consumption, and thus more likely to risk harm to consumers than the objective speech of disinterested third parties, like physicians.¹⁶⁴ However, independent speech can be dangerous too “because listeners are less likely to be skeptical of recommendations made by objective observers.”¹⁶⁵ As weak as it may be, this particular argument about bias and skepticism would seem to apply equally to Offixa and Notixa, since in either case a self-interested seller makes a claim to the safe and effective use of a product, which has not been approved by the FDA.

Here again, the stronger argument is the formalist one. The law often imposes special duties to speak, or not speak, on those who create risks, such as product makers or landowners.¹⁶⁶ Indeed, here the FDA reiterates that it is regulating the particular conduct of selling a drug, which explains why the speech of non-sellers is irrelevant—they are not undertaking the relevant

¹⁶¹ See *Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices*, U.S. FOOD & DRUG ADMIN. (Jan. 2009), <https://www.fda.gov/RegulatoryInformation/Guidances/ucm125126.htm> [<https://perma.cc/VQ7MTPL4>]; see also Aaron S. Kesselheim & Jerry Avorn, *The Food and Drug Administration Has the Legal Basis To Restrict Promotion of Flawed Comparative Effectiveness Research*, 31 HEALTH AFF. 2200, 2201 (2012) (discussing some of these safe harbors).

¹⁶² See *Va. State Bd. of Pharmacy v. Va. Citizens Consumer Council, Inc.*, 425 U.S. 748, 765 (1976) (“[T]he free flow of commercial information is indispensable.”).

¹⁶³ See *Law*, *supra* note 22, at 933 (arguing against an interpretation of the First Amendment that would exclude emotive noninformational advertising per se).

¹⁶⁴ See *REDISH*, *supra* note 30, at 116 (discussing the rationale of the Supreme Court in *Sorrell v. IMS Health*).

¹⁶⁵ *Id.*

¹⁶⁶ See, e.g., *Braaten v. Saberhagen Holdings*, 198 P.3d 493, 504 (Wash. 2008) (limiting the duty to warn to the manufacturer’s own products).

conduct of introducing a misbranded drug into interstate commerce. Similarly, for illicit drugs, non-sellers can say all sorts of things about cocaine (“*mmm*, what a great high that would be”), without facing liability for transporting the drug in interstate commerce, as long as they do not undertake the latter behavior.

An Offixa may be discovered by physicians, who begin using a drug’s side effect as a treatment, or who reason by analogy that a drug may be helpful in another domain where it is not FDA approved. Physicians face no liability for using a drug off-label,¹⁶⁷ though a company will if it starts promoting the same use. Similarly, physicians can drive Notixa consumption. Physicians freely recommend the vitamin B6 to take along with a drug for tuberculosis, red yeast extract as a natural statin for cholesterol treatment, vitamin D for osteoporosis, bananas for renal tubular disorder, fiber for irritable bowel syndrome, sugar substitutes for diabetes, lactase supplements for digestive disorders, and prenatal vitamins to prevent neural tube disorders. Any of these could be no-label drugs if their makers expressed an intent to use them to treat a disease. The regime is quite parallel for both Offixa and Notixa.

Overall, then, for either Offixa or Notixa, manufacturers commit a crime if they promote the product for cancer, and in both cases there will be others who make the same claims but face no criminal liability, because they do not ship the product in interstate commerce.¹⁶⁸ If the First Amendment forbids this sort of “discrimination” between those who act and those who do not, it applies equally to Offixa or Notixa.

G. The Alternative To Regulate Consumption Behavior

Seventh, challengers argue that it is perfectly legal for a doctor to prescribe a drug off-label and a patient to consume it.¹⁶⁹ Thus, unlike a speaker who proposes a crime like murder, the company’s encouragement of legal activity is protected by the First Amendment. A similar argument could be made in the Notixa domain: individuals may be perfectly free to take industrial bleach for their allergies (as in the case discussed in Part II above), but the sellers of those unapproved products commit a crime if they market them with an intent that they be so used. The fact that speech concerns a legal activity is necessary, but not sufficient, for it to be protected by the First Amendment.¹⁷⁰

¹⁶⁷ See, e.g., *Weaver v. Reagen*, 886 F.2d 194, 200 (8th Cir. 1989) (holding that Medicaid must reimburse off-label uses of AZT drug).

¹⁶⁸ See *supra* Part III.A.

¹⁶⁹ See, e.g., *Smolla*, *supra* note 101, at 89 (suggesting that the FDA is encroaching on the regulation of the legally available drugs that doctors choose to prescribe).

¹⁷⁰ See *Law*, *supra* note 22, at 942 (“Tobacco and alcohol manufacturers . . . argue that if a product is legal then any advertising promoting it is necessarily protected by the First Amendment. This claim, however, is . . . unsustainable.”).

A more interesting argument suggests that if the federal government is so concerned about off-label drug use, then it *should* directly regulate the consumption of drugs themselves, by regulating the *behavior* of physicians or patients rather than the *speech* of manufacturers.¹⁷¹ This argument fits into constitutional doctrine, which sees the regulation of speech as a last resort, allowed only when the regulation of behavior fails.¹⁷² The notion that a behavior regulation is possible shows that regulation of speech is inappropriate.¹⁷³

There is some irony to this argument, since the FDA maintains that it is regulating the *conduct* of selling a misbranded and unapproved drug in interstate commerce.¹⁷⁴ And, there are cogent explanations for why Congress chose to regulate manufacturers, who are engaged in interstate commerce, rather than patients or doctors who are engaged in purely local activity.¹⁷⁵ Aside from the values of federalism, manufacturers are in the best position to undertake the science that would prove the safety and efficacy of these uses and to recoup those costs if successful.¹⁷⁶ Moreover, the plan created by Congress allows doctors and patients to experiment with unproven uses, even while maintaining an incentive for manufacturers to study them more systematically. Whether Congress *could* change the FDCA to regulate the practice of medicine directly is an interesting question, far beyond the present inquiry.

It is not particularly clear *how* this supposed alternative mechanism of conduct-based regulation would work, since the regulator must still discern whether a given product is being sold, prescribed, or consumed for an unapproved use versus an approved use. Could a regulator extract the

¹⁷¹ See, e.g., Bambauer & Bambauer, *supra* note 30, at 360 (“The principal implication of info-libertarianism is that it prefers direct regulation of conduct to achieve regulatory goals over indirect regulation of information.”); Klasmeier & Redish, *supra* note 90, at 343 (“[I]f the FDA were truly concerned with the manufacturer’s non-expressive act of sale with intent that the product be used off-label, it would logically prohibit *all* sales of a drug widely used off-label.”); Noah, *supra* note 106, at 32 (arguing that direct controls over off-label drug use do not raise free speech obstacles).

¹⁷² Bambauer & Bambauer, *supra* note 30, at 360–61.

¹⁷³ The Supreme Court has sometimes turned this argument on its head. See, e.g., *Posadas de P.R. Assocs. v. Tourism Co. of P.R.*, 478 U.S. 328, 346 (1986) (stating that it would “surely be a strange constitutional doctrine which would concede to the legislature the authority to totally ban a product or activity, but deny to the legislature the authority to forbid the stimulation of demand for the product or activity through advertising”); see also Law, *supra* note 22, at 938 (calling it “flatly inconsistent with a settled body of First Amendment jurisprudence” for a state to be able to “suppress speech advocating conduct that it could prohibit”); Frederick Schauer, *Commercial Speech and the Architecture of the First Amendment*, 56 U. CIN. L. REV. 1181, 1182 (1988) (proposing that *Posadas* is irreconcilable with *Virginia Citizens Consumer Council* and *Central Hudson*).

¹⁷⁴ See *supra* notes 1–2 and accompanying text and discussion *supra* Part III.A.

¹⁷⁵ See David Orentlicher, *Off-Label Drug Marketing, the First Amendment, and Federalism*, 50 WASH. U. J.L. & POL’Y 89, 98–101 (2016).

¹⁷⁶ See discussion *supra* Part III.E.

physician's intended use for a product from his notes in the patient's electronic medical records?¹⁷⁷ That data is a form of speech too.¹⁷⁸ If the regulation targets the doctor's recommending or prescribing of the drug, it would seem to be an even more direct regulation of speech.

Supposing that there is some nonspeech way to regulate off-label use, and that counts as a critique of the status quo, this seventh point would seem to apply equally to drugs that have received no FDA approvals (Notixa). An alternative regulatory system could allow unapproved drugs to be advertised and shipped in interstate commerce (as they were prior to FDCA being enacted), but then prohibit doctors from recommending them or patients from consuming them. Patients would have less liberty to try drugs than they do now and there would be more federal interference in local behavior. And, without a solution to the collective action problem, we would likely have much less science produced and thus less real information about safety and efficacy. As irrational as the alternative nonspeech regulation of no-label drug use may be, it may also be conceptually possible, just as much as the nonspeech regulation of *off*-label use may be conceptually possible.

Thus the regulation of Offixas and Notixas rise and fall together on this final argument. This criterion does not cut between them.

IV. CONCLUSIONS

The analysis here shows that the challenges to the FDA in the off-label domain are actually more profound than they appear. If these arguments rest on valid premises, the same premises would threaten the entire FDA premarket approval regime. Indeed, the companion article shows that virtually every area of federal law has an intent-based test, not unlike the one in the FDCA.¹⁷⁹ And,

¹⁷⁷ See Ryan Abbott & Ian Ayres, *Evidence and Extrapolation: Mechanisms for Regulating Off-Label Uses of Drugs and Devices*, 64 DUKE L.J. 377, 380–81 (2014) (arguing for use of prescribing data by FDA); Andrew English et al., *A New Regulatory Function for E-Prescriptions: Linking FDA to Physicians and Patient Records*, in FDA IN THE TWENTY-FIRST CENTURY: THE CHALLENGES OF REGULATING DRUGS AND NEW TECHNOLOGIES 486, 486 (Holly Fernandez Lynch & I. Glenn Cohen eds., 2015) (arguing for such use more generally to “serve FDA regulatory objectives in overseeing the postmarket [sic] safety and efficacy of medical products”); Marc A. Rodwin, *Rooting Out Institutional Corruption To Manage Inappropriate Off-Label Drug Use*, 41 J.L. MED. & ETHICS 654, 659 (2013) (arguing for use of prescribing data by FDA); Benjamin N. Roin, *Solving the Problem of New Uses* 63 (Oct. 1, 2013) (unpublished manuscript), <http://ssrn.com/abstract=2337821> [<https://perma.cc/92TK-3BFB>] (proposing use of electronic medical records in this way).

¹⁷⁸ See *Sorrell v. IMS Health Inc.*, 564 U.S. 552, 570 (2011) (“[T]he creation and dissemination of information are speech within the meaning of the First Amendment.”); Jane Bambauer, *Is Data Speech?*, 66 STAN. L. REV. 57, 57 (2014) (answering her question in the affirmative).

¹⁷⁹ See generally Robertson & Laurion, *supra* note 32.

in case after case, the courts are routinely using speech as evidence of the relevant intent.¹⁸⁰

So what? One could assert a slippery slope argument in a consequentialist sense: that judicial recognition of a right to off-label promotion will inevitably lead courts to also someday strike down the FDA's entire premarket approval regime and perhaps many other federal laws with a similar intent-based structure. That prognostication may be true given the way precedent works, and many may adjust that outcome horrible. Yet, such a consequentialist argument would require additional premises about judicial behavior, not offered here.¹⁸¹ To the contrary, courts can and do draw arbitrary lines, and the Supreme Court can and does simply refuse to take cases that would undermine an arbitrary but workable status quo.¹⁸²

The point is instead about principle. The current debate over off-label promotion is implicitly, and sometimes explicitly, a debate about competing theories of the First Amendment.¹⁸³ However, it is rare for such theories to be comprehensively articulated or evaluated as such; instead, we only see glimpses through inevitably ambiguous rhetoric and argued (favorable) applications to specific cases. But how are we to evaluate whether the premises themselves are reasonable? How can we evaluate if a given First Amendment theory is legitimate?

As Richard Fallon and Mitchell Berman have argued—drawing from the philosophical approach of John Rawls and the pragmatists—the analytic crucible is a reflective equilibrium with our other judgments.¹⁸⁴ If a theory of

¹⁸⁰ See *supra* notes 81–84 and accompanying text.

¹⁸¹ See Eugene Volokh, *Slippery Slope Arguments*, in 8 THE INTERNATIONAL ENCYCLOPEDIA OF ETHICS 4923, 4924 (Hugh LaFollette ed., 2013) (“[O]verstated slippery slope arguments, which claim that ‘Adopting proposed decision A will necessarily lead to the adoption of decision B,’ are generally fallacious. . . . To be valid, . . . [t]he argument would have to assert that, though a line between A and B could be drawn, for political, economic, or psychological reasons it may end up not being drawn.”). See generally DOUGLAS WALTON, *SLIPPERY SLOPE ARGUMENTS* (1992) (arguing that some forms of slippery slope arguments are valid).

¹⁸² See Toni M. Massaro, *Constitutional Law as “Normal Science,”* 21 CONST. COMMENT. 547, 548 (2004) (“Simulating the common law process of decision-making, the Justices invoke available doctrinal support for shifts. They seek to cabin the impact of any changes, and they emphasize the limited role that the Court realistically can, and constitutionally should, play in shaping public policy.”).

¹⁸³ See, e.g., Klasmeier & Redish, *supra* note 90, at 350–51 (describing “four core postulates” of the First Amendment).

¹⁸⁴ See Mitchell N. Berman, *Reflective Equilibrium and Constitutional Method: Lessons from John McCain and the Natural-Born Citizenship Clause*, in THE CHALLENGE OF ORIGINALISM: THEORIES OF CONSTITUTIONAL INTERPRETATION 246, 247 (Grant Huscroft & Bradley W. Miller eds., 2011); Richard H. Fallon Jr., *Arguing in Good Faith About the Constitution: Ideology, Methodology, and Reflective Equilibrium*, 84 U. CHI. L. REV. 123, 123–24 (2017).

the First Amendment necessary to support a right to off-label promotion also creates a right for fraudsters to bring drugs to market without FDA approval at all (and jeopardizes large swaths of federal law, as we show in the companion piece), then our views about these applications can shed light back on the theory itself. If my argument is valid, there does not seem to be a basis for off-label exceptionalism. One must either accept a right to no-label drug promotion or reject a right for off-label drug promotion.¹⁸⁵ Concededly, the present negative form of the argument cannot say which is the more bitter pill. Even for strong libertarians, however, such an implication may give pause.¹⁸⁶ This Article shows how high the stakes may be for the project of using the Constitution to dismantle the modern regulatory state.

¹⁸⁵ In formal logic, the relationship is *modus tolens*. In informal logic, the argument is known as a *reductio ad absurdum*. See generally Candice Shelby, *Reductio Ad Absurdum and Slippery Slope Arguments: Two Sides of the Same Coin?*, 1 *ANNALES PHILOSOPHICI* 77, 79–80 (2010) (showing that the *reductio* is valid even while the slippery slope argument often is not).

¹⁸⁶ See, e.g., Epstein, *supra* note 4, at 20 (“For the moment, at least, I would leave in place the requirement that a drug pass Phase I trials.”).